REMARKS

Applicants would first like to thank Examiner Shin and Primary Examiner Angell for their time and helpful suggestions during the telephonic interview with the undersigned and one of the inventors, Dr. James Donegan on November 27, 2007. During the interview, the pending claims and prior art were discussed. The substance of the interview will be referred to throughout this response.

Claims 275 and 283-295 are pending in the current application. Claims 283-288 and 295 have been canceled in order to advance prosecution. Claim 275 has been amended to more distinctly claim that which Applicants regard as the invention. Applicants note that the subject matter of claim 295 has been incorporated into claim 275. Applicants reserve the right to file subsequent continuation/divisional applications to subject matter originally recited in claim 275 and 283. The claim amendments will be discussed in further detail below. Claims 296-301 have been added to recite specific embodiments.

1. Claim Objections

Claim 275 is objected to for containing non-elected subject matter: antibody, cellular matrix, polysaccharide, and polypeptide. In response, claim 275 has been amended to delete references to antibody, cellular matrix, polysaccharide and polypeptide.

Claim 295 is objected to because of the following informalities: the alignment of lines in claim 295 triggers a question whether some claim language is missing in the claim. Consistent alignment of lines is required. As noted above, claim 295 has been canceled.

In view of the amendment to claim 275 and the cancellation of claim 295, Applicants assert that the objection to claims 275 and 295 have been overcome. Therefore, Applicants respectfully request that the objection be withdrawn.

2. The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 275, 283, and 295 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action specifically

states:

> The clams are drawn to a multimeric composition comprising a receptor binding protein. There is no disclosure of the claimed subject matter "receptor binding protein" in the specification. Although the specification discloses the term "ligand binding receptor", it is completely silent about the claimed "receptor binding protein", and there is no indication in the specification that the term "ligand binding protein" is synonymous or interchangeable with the term "receptor binding protein". Further, nowhere in the specification is it described that the first element comprises a receptor binding protein. Accordingly, the claims introduce new matter that was not described in the specification at the time the application was filed.

Applicants respectfully traverse the rejection and believe that there was sufficient support for "a receptor binding protein". In Applicants' view, the term "receptor binding protein" is a term that basically recites a "protein that binds to a receptor" ; i.e a protein ligand that binds to its cognate receptor and that this has numerous antecedents in the specification as cited above. However, as discussed during the interview on November 27, 2007, claim 275 has been amended to recited that the first element is "a ligand to a cell surface receptor". This phrase, as further discussed during the interview, is supported by the specification on page 71, page 12, which states that the compound in the first element of the monomeric unit could be a ligand. The following definition of "ligand" is provided on the first full paragraph of page 41.

> Ligands or chemical modifications, being any chemical entity, natural or synthetic, which can be utilized in this invention include macromolecules greater than 20,000 m.w. as well as small molecules less than 20,00 m.w. The ligands or ligands can include both macromolecules and small molecules. Macromolecules which can be utilized include a variety of natural and synthetic polymers including peptides and **proteins**, nucleic acids, polysaccharides, lipids, synthetic polymers, including polyanions polycations and mixed polymers. Small molecules include oligopeptides, oligonucleotides, monosaccharides, oligosaccharides, and synthetic polymers, including polyanions polycations and mixed polymers. Small molecules include mononucleotides, oligonucleotides, oligopeptides, oligosaccharides,

> monosaccharides, lipids, sugars, and other natural and synthetic entities.

It can be seen that the term "ligand" was meant very broadly and encompassed any entity for which there would be a corresponding binding partner, i.e a ligand receptor. In this sense a "receptor binding protein" would be the subgroup from above where the ligand is a protein.

In describing cell targeting entities and their corresponding receptors, page 42, line 8 refers to

> c) ligands which have affinity for cell surfaces. These include hormones, lectins, proteins, oligosaccharides and polysaccharides. Asialoorosomucoid, for example, binds to the cellular asialogycoprotein receptor (references deleted) and transferring binds to transferring cellular receptors..

It should be noted that some of the ligand pairs that were previously described are in accordance and exemplify this term, "ligand to a cell surface receptor". Specifically, lymphokines, cytokines, hormones and growth factors which were originally part of claim 275, represent proteins that are ligands of cell surface receptors. As such, it can be said that the originally filed claim described a group of proteins that bind to a receptor (and therefore are "receptor binding proteins") and they also encompass a group of proteins that can be collectively described as "ligands to cell surface receptors" since these are all moieties that can bind to a cell surface by interacting with membrane bound receptors. Applicants note that hormones, cytokines and growth factors are recited in new claims 296-301.

Applicants note that claims 283 and 295 have been canceled to advance prosecution.

In view of the amendment of claim 275 and cancellation of claims 283 and 295, Applicants assert that the rejection of claims 275, 283 and 295 under 35 USC 112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

3. The Rejections Under 35 USC 112, Second Paragraph

Claims 275 and 283 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Office Action specifically states:

> Claim 275 recites the limitations "wherein said first element" in lines 2-3 "said second element is" in line 5, "wherein said monomeric units" in line 7. There is insufficient antecedent basis for these limitations in the claim.
>
> Claim 283 recites the limitation "wherein more than one protein of the first element of said monomeric unit" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim because claim 275 does not recite "more than one protein of the first element" ;rather, claim 275 expressly recites "wherein said first element is protein", indicating that the first element comprises only one protein, not more than one.

Applicants respectfully traverse the rejection. However as discussed during the interview on November , in order to advance prosecution, claim 275 has been amended to recite

> A multimeric composition comprising more than one monomeric unit **wherein each monomeric unit** comprises two elements **covalently attached to one another wherein a first element** is a ligand to a cell surface receptor, **wherein a second element** is a polynucleotide **and wherein each monomeric unit is attached to a binding matrix...**

Claim 283 has been canceled.

In view of the amendment of claim 275 and the cancellation of claim 283, Applicants assert that the rejection of claims 275 and 283 under 35 USC 112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

4. The Rejection Under 35 USC 102

Claims 275 and 283 are rejected under 35 U.S.C. 102(b) as being anticipated by Engelhardt et al. (US 5,288,609).

Applicants respectfully traverse the rejection. As noted above and as discussed during the interview on November 27, 2007, Applicants note that the subject matter of claim 295 has been incorporated into claim 275. Claim 295 was not included in this rejection. Further, as noted in the Office Action, Engelhardt does not disclose hydrogen binding between the monomeric unit and binding matrix. Further discussion distinguishing the

claimed invention from Engelhardt is provided below in response to the rejection under 35 USC 103. As discussed above, Applicants note that claim 283 has been canceled.

In view of the above arguments and amendment of claim 275 and cancellation of claim 283, Applicants assert that the rejection of claims 275 and 283 under 35 USC 102 have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

5. The Rejection Under 35 USC 103

Claims 275,283, and 295 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Engelhardt et al. (US 5,288,609), further in view of Takeda et al. *(PNAS,* 1992, 89:8180-8184). The Office Action specifically states:

> The claims are drawn to a multimeric composition comprising a receptor protein and a polynucleotide wherein the protein and the polynucleotide are attached to a binding matrix via hydrogen bonding, wherein the binding matrix is polynucleotide.
>
> Engelhardt et al. teach a polynucleotide complexed with a receptor protein, wherein the complexed particle is attached to a matrix. They teach that the polynucleotide can be covalently or noncovalently attached to the particle through a moiety, preferably polynucleotides, wherein the particle is a binding matrix such as glass, a polymeric material, or biological cells. They also teach that essentially any receptor can be utilized to complex the polynucleotide with the particle, wherein the receptor includes a hormone (columns 5-6). Engelhardt et al. do not teach that the protein and polynucleotide are attached to the matrix via hydrogen bonding.
>
> Takeda et al. teach that protein-DNA complex interaction is mediated primarily by hydrogen bonding, which contributes to the stability of the protein-DNA complex (page 8180).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the hydrogen bonding of Takeda et al. into the complex of protein and polynucleotide of Engelhardt et al.
>
> One of ordinary skill in the art would have been motivated to attach or complex the receptor protein and the polynucleotide of Engelhardt et al. by means of hydrogen

> bonding of Takeda et al., because Takeda et al. clearly teach that hydrogen bonds are formed between amino acids and DNA bases and that the hydrogen bonds contribute to the stability of the DNA-protein complex (page 8180), thereby achieving a more stable multimeric composition comprising a receptor protein-polynucleotide complex attached to a polynucleotide matrix, as claimed in the instant case. Since a means to improve stability of DNA-protein complex was known in the art as taught by Takeda et al., and since the multimeric composition comprising a receptor protein and a polynucleotide attached to a binding matrix was available in the art as taught by Engelhardt et al., the skilled artisan would have had a reasonable expectation of success in combining the teachings of the prior art. Accordingly, the instantly claimed invention taken as a whole would have been ***prima facie*** obvious at the time of filing.

Applicants respectfully traverse the rejection. As discussed during the interview on November 27, 2007, Applicants disagree with the characterization of the Office Action. In the present invention, a monomeric unit is made up of a first element (a protein which is a ligand to a surface receptor) and a second element (a polynucleotide) where the monomeric subunit is attached to a matrix through a noncovalent interaction (hydrogen bonding) between the second element and the matrix. Claim 275 has been amended to recite that the matrix is also a polynucleotide and that each monomeric unit is attached to the binding matrix via hydrogen binding. In contrast, it appears that in the Office Action, the matrix in Engelhardt was considered to be the particle.

Further, although, the use of a receptor is cited as an example of means for binding to a particle (matrix) in Engelhardt, and as such a monomeric subunit can be considered to comprise a polynucleotide and a receptor, the attachment to the particle is not carried out through the second element (the polynucleotide) as recited in claim 275, but rather through a receptor /ligand interaction, and as such, attachment in Engelhardt is through the first element not the second element. In short, when a receptor is used in conjunction with a polynucleotide Engelhardt, the receptor is used for non-covalent attachment to a particle. In the case of column 6 in Englehardt where a nucleic acid binds noncovalently to a particle (through complementary base pairing) the requirement of a polymeric second element carrying out attachment is met, but there is a lack of a protein that is a ligand to a surface receptor as the first element. Thus, there

is a lack of correspondence in Engelhardt for the nature of the first and second elements and their role in attachment to a particle (matrix).

Applicants further note that claim 275 has been amended to recite that the first element and second element of the monomeric unit are covalently attached to each other". This amendment is supported by the specification on page 71, five lines from the bottom where it is stated:

> "The polymers can be attached to the compounds either covalently or non-covalently."

In contrast in Engelhardt, the first and second elements appear to be attached to each other via non-covalent interaction.

In summary, the claimed invention can be distinguished from Engelhardt in several respects. First, in contrast with Engelhardt, the binding matrix of the present invention is a polynucleotide; secondly, the attachment of the monomeric unit to the binding matrix in the complex of the present invention occurs via through the second element via hydrogen bonding as opposed to the first element and in the composition of the present invention.

The Office Action further recites the inclusion of the reference of Takeda to include the concept of non-covalent binding between a protein and a polynucleotide. In this case the cre protein is being considered to be the equivalent of a receptor and it is bound to a DNA molecule. However, if the cre protein is the first element, it would be assumed that the DNA is the second element.

The only thing that Takeda teaches is interaction of a protein with a specific nucleic acid sequence and there is no indication in the Office Action of any particular purpose served by inclusion of the Cre protein in the method taught by Engelhardt. No indication is given of why an enhancement of stabilization between this protein and a nucleic acid would achieve a more stable multimeric composition since the basis of the multimerization is nucleic acid hybridization between complementary pairs. In short, there is no indication at all of what purpose the inclusion of the cre protein serves and there is a total lack of motivation to carry out the combination described by the Office Action. All that is given in the Takeda reference is an indication that the binding of cre to the nucleic acid will be stable. Therefore, it is questionable as to whether there would be motivation to combine Engelhardt and Takeda.

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As noted above, claim 275 has been amended to recite that the first element and second element are attached to each other via **covalent** interactions. Therefore the addition of Takeda does not serve any purpose.

Applicants note that claims 283 and 295 have been canceled to advance prosecution.

Even assuming arguendo, that there would have been motivation to combine Engelhardt and Takeda, the claimed composition could not have been obtained for a number of reasons. First, in Engelhardt, the first element not the second element of the monomeric unit was bound to the binding matrix. Secondly the protein in Takeda was **noncovalently** bound to the nucleic acid. At best the combination of Engelhardt and Takeda would result in a composition comprising a monomeric unit where the first element is bound to the matrix via a receptor/ligand interaction and the first and second elements of the monomeric unit are bound to each other via non-covalent interactions.

In view of the above arguments, amendments to claim 275 and cancellation of claims 283 and 295, Applicants assert that the rejection of claims 275, 283 and 295 under 35 USC 103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

SUMMARY AND CONCLUSIONS

Claims 275, 283 and 295 are presented for further examination. Claims 275 have been amended; claims 296-301 have been added. Claims 283 and 295 have been added.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

Cheryl H. Agris

Date: 12/3/07

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